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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,872	05/19/2006	Ilia Fishbein	RCHP-135US	1203

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
05/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,872	FISHBEIN ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-37,39 and 40* is/are pending in the application.

4a) Of the above claim(s) *2,4-6, and 11-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,8-10,33-37,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 09, 2009 has been entered.

Claims 7 and 38 are cancelled. Claims 39 and 40 are newly added. Claims 1-6, and 8-37, 39, and 40 are pending. Claims 1, 3, 8-10, 33-37, 39, and 40 are currently under examination.

Claims 2, 4-6, and 11-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

This application 10/567,872 is a 371 of PCT/US04/26509 filed on 08/13/2004, which claims benefit of 60/494,886 filed on 08/13/2003.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Previous rejection of claim 33 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because the claim has been amended.

Claim 33 has been amended and no longer recites "wherein the modified protein comprises at least one of a fusion protein and a polypeptide".

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Previous rejection of claims 1, 3, 8, 10, 33, 38, and 39 under 35 U.S.C. 102(b) as being anticipated by Halbreich et al. (U.S. patent No. 6,150,181, issued Nov. 21, 2000), is ***withdrawn*** because upon further consideration Halbreich et al. does not explicitly disclose word "metal" in the context of magnetic nano-particles (mean diameter 9 nm) named ferrofluid (FF), which is made of the ferrites MFe_2O_4 (including magnetite Fe_3O_4) and maghemite γ Fe_2O_3.

4. Previous rejection of claims 1, 8-10, 33, and 38 under 35 U.S.C. 102(b) as being anticipated by Feijen et al. (U.S. patent No. 4,634,762, issued Jan. 6, 1987), is ***withdrawn*** because upon further consideration Halbreich et al. does not explicitly disclose word "metal" in the context of coating a surface of a medical device and the conjugates are covalently bonded conjugates of an anticoagulant and protein that are prepared in the presence of a coupling agent that forms amide linkages between the anticoagulant and the protein.

5. Claims 1, 3, 8-10, 33, 39, and 40 are rejected under 35 U.S.C. 102(e) and 102(a) as being anticipated by **Levy et al.** (U.S. 2003/0044408, publication date, 03/06/2003, filed on 06/14/2000; this reference is cited in the IDS filed by Applicant on 08/20/2008).

Claim 1 is directed to a composition comprising a metal surface and a modified protein covalently bound to the metal surface. Claim 8 further limits the metal surface being a surface of a medical device. Claim 9 further limits claim 8 to medical device selected from the group consisting of a stent, a heart valve, a wire suture, a joint replacement, a urinary dilator, an orthopedic dilator, a catheter and an endotracheal tube. Claim 10 further limits claim 8 to the medical device being at least one of an internal device and an external device. Claim 33 limits the modified protein to comprise a fusion protein or a polypeptide. Newly added claim 39 is directed to a composition comprising a layer of modified protein covalently bound to a functional group of a compound that is covalently linked to a metal surface of medical device. Claim 40 further limits claim 39 with the compound covalently linked to the metal surface being a bisphosphonate compound.

With regard to limitations of claims 1, 8 and newly added claim 39, Levy et al. teaches a therapeutic delivery system efficiently introduces biologically active molecules to mammalian cells without the use of synthetic polymers or biopolymer coatings. Surface modification of a metal support, such as a such as stainless steel and titanium medical devices, results in a single molecular layer that can fasten various molecules, thereby minimizing any cellular inflammatory response while enhancing biocompatibility (See abstract, and paragraph [0003], Levy et al., 2003). Levy et al. teaches that the paired component which is most suitable for attachment to the surface-modified metal would be immobilized. The component is covalently cross-linked to a monomeric or polymeric surface modifier, which, in turn, provides chemical moieties that bind to the metal surface (See abstract, and paragraph [0026] and [0037], Levy et al., 2003). .

With regard to the limitation "wherein the modified protein is covalently bound to the metal surface through thiol residue and a linker" recited in claim 3, Levy teaches that in Fig. 2 depicts a reaction scheme for modifying surfaces of metal supports via amino group containing bisphosphonates. During an activation step, the N-succinimidyl ester group in SPDP (N-succinimidyl-3-(2-pyridyl- dithio)-propionate) reacts with the amino group of a chemosorbed polyamino-bisphosphonic acid, to activate a steel surface with a pyridyldithio group, and during a modification step, a thiol modified antibody is chemically linked to the metal (See paragraph [0013], US 2003/0044408. Levy et al, 2003).

With regard to the limitation of medical devices recited in claim 9 and the limitation of internal device and external device recited in claim 10, Levy et al. teaches that medical devices may include non-orthopedic devices, temporary placements and permanent implants, such as tracheostomy devices, intraurethral and other genitourinary implants, stylets, dilators, stents,

vascular clips and filters, pacemakers [which reads on internal device], wire guides and access ports of subcutaneously implanted vascular catheters [which reads on external device]. (See paragraph [0036], US 2003/0044408. Levy et al, 2003).

With regard to the limitation "wherein the modified protein comprises a fusion protein or a polypeptide" recited in claim 33, Levy et al. teaches the composition comprises a biologically active molecule. In another aspect of the invention, the biologically active molecule is preferably one component of an affinity pairing system, and still preferred, the biologically active molecule is avidin or biotin; IgG or protein A; or transferrin or its receptor (See paragraph [0008], US 2003/0044408. Levy et al, 2003).

With regard to the limitation "wherein the compound covalently linked to the metal surface is a bisphosphonate compound" recited in newly added claim 40, Levy teaches that in Fig. 1 shows the general chemical structure of a monomeric or polymeric functionalized biophosphonate suitable for the modification of metal surfaces to bind proteins thereon (See abstract, and paragraph [0012], Levy et al., 2003).

Thus, Levy et al. clearly anticipate claims 1, 3, 8-10, 33, 39, and 40 of instant application.

The Examiner notes that Applicant's arguments regarding the modified protein recited in claim 1 has to be covalently bound to the metal surface directly (See below Applicant's arguments in the maintained 102(e) rejection anticipated by Kutryk et al.) have been fully considered and found not persuasive. The Examiner's response to Applicant's arguments in this regard (See below Response to Applicant's arguments in the maintained 102(e) rejection

anticipated by Kutryk et al.) is relevant to the rejection anticipated by Levy et al. documented above in this office action. It is worth noting that the cross-liner/coupling agent SPDP disclosed in Fig. 1B of instant application is identical to the cross-liner/coupling agent SPDP (N-succinimidyl-3-(2-pyridyl- dithio)-propionate) taught by Levy et al. In other words, both claimed compositions and the composition taught by Levy et al. (as well as the composition taught by Kutryk et al., see below) require utilization of a cross-liner/coupling agent to mediate the formation of covalent bond between modified protein and metal surface of a medical device.

6. Claims 1, 8-10, and 33 remain rejected and newly added claim 39 is rejected under 35 U.S.C. 102(e) as being anticipated by Kutryk et al. (U.S. patent No. 7,037,332, issued May 2, 2006, filed on 03/15/2001). Applicant's arguments filed 03/09/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 7-8 of the office action mailed on 05/22/2008.

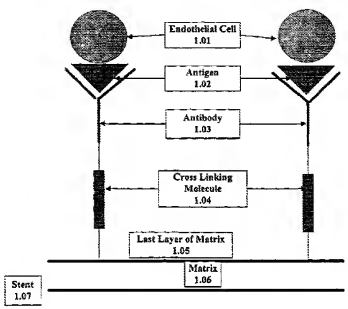
For clarity and completeness of this office action, the rejection for the reasons of record advanced on page 7-8 of the office action mailed on 05/22/2008, is revised below to address claim amendments filed on 03/09/2009.

Claim 1 is directed to a composition comprising a metal surface and a modified protein covalently bound to the metal surface. Claim 8 further limits the metal surface being a surface of a medical device. Claim 9 further limits claim 8 to medical device selected from the group consisting of a stent, a heart valve, a wire suture, a joint replacement, a urinary dilator, an orthopedic dilator, a catheter and an endotracheal tube. Claim 10 further limits claim 8 to the medical device being at least one of an internal device and an external device. Claim 33 limits

the modified protein to comprise a fusion protein or a polypeptide. Newly added claim 39 is directed to s composition comprising a layer of modified protein covalently bound to a functional group of a compound that is covalently linked to a metal surface of medical device.

With regard to the limitations of claims 1 and 8, Kutryk et al. teaches a composition comprising a medical device coated with one or more antibodies and one or more layers of a matrix, and the matrix may be noncovalently or covalently attached to the medical device, and antibodies may be covalently attached to the matrix using hetero- or homobifunctional cross-linking reagents (See abstract, lines 1-4, column 5, lines 15-55, column 12, and Figure 1, Kutryk et al.). Kutryk et al. further teaches that stents can be composed of metallic structural elements onto which the matrix is applied (See lines 22-24, column 8, Kutryk et al.) and it will be apparent to those skilled in the art that other self-expanding stent designs (such as resilient metal stent design) could be used with the antibodies and matrices (See lines 37-40, column 8. Kutryk et al.).

Figure 1



With regard to the medical device recited in claim 9, and the limitation "wherein the medical device is at least one of an internal device and a external device" recited in claim 10, Kutryk et al. teaches "medical device" refers to a device that is introduced temporarily or permanently into a mammal for the prophylaxis or therapy of a medical condition. These devices include any that are introduced subcutaneously, percutaneously or surgically to rest within an organ, tissue or lumen, which is encompassed by the limitation an internal device recited in claim 10. Medical devices may include, stents, synthetic grafts, artificial heart valves, permanent drug infusion catheters, embolic coils, embolic materials used in vascular embolization (e.g., PVA foams), and vascular sutures. (See lines 50-62, column 5, Kutryk et al.). Kutryk et al. also teaches using the medical device for endothelial cell binding assay, which is encompassed by the limitation an external device recited in claim 10 of instant application.

With regard to the limitation "wherein the modified protein comprises a fusion protein or a polypeptide" recited in claim 33, the reasonable interpretation of "modified protein" and "a polypeptide" recited in claim 33 reads on the antibody crossed-linked onto the metal surface of medical device such as a stent taught by Kutryk et al.

With regard to the limitation "a functional group of a compound that is covalently linked to a metal surface of a medical device" recited in newly added claim 39, Kutryk et al. teaches that the linker molecules provide the matrix with a number of functionally active groups that can be used to covalently couple one or more types of antibody (See lines 23-25, column 12, Kutryk et al.).

Thus, Kutryk et al. clearly anticipate claims 1, 8-10, 33, and 39 of instant application.

Applicant's arguments

Applicant argues that the antibodies taught by Kutryk are not covalently bound to a metal surface directly, and the antibodies are cross-linked to a matrix which forms a "coating" on the surface. (Kutryk Abstract, col. 12, lines 15-23). Applicant argues that the matrix is "coated" onto the medical device as described in Kutryk, column 10, lines 15-29, as follows: "The stent is dipped or sprayed with a liquid solution of the matrix of moderate viscosity." col. 10, lines 24-26. Applicant argues that in Applicants' claims, "the modified protein is covalently bound to the surface." (paragraph [0016]), and the surface of the metal device is modified with a surface modifier that chemically coordinates, i.e., is covalently linked, with the metal surface. (Paragraphs [0041] - [0044], [0066]). Applicant argues that, as shown in Figure 1B, the surface is then reacted with a compound such as SPDP to create reactive groups on the surface modifier.

These reactive groups covalently bind to the modified protein. Applicant argues that, thus, unlike the invention of Kutryk, the modified protein is covalently bound to the reactive groups of the surface modifier, which is chemically coordinated, i.e., covalently bound, with the metal surface. Neither the surface modifier nor the protein is a "coating." Therefore, the modified protein is directly "covalently bound to the metal surface." (See pages 9-10 of Applicant's remarks filed on 03/09/2009).

Response to Applicant's arguments

Applicant's arguments that the claimed composition requires "the modified protein is directly covalently bound to the metal surface" have been fully considered and found not persuasive. First, Applicant's arguments are *in direct contraction* with (i) claim 3 which recites "wherein the modified protein is covalently bound to the metal surface through a thio residue and a linker, and (ii) the newly added claim 39 which reads as "A composition comprising a layer of modified protein covalently bound to a functional group of a compound that is covalently linked to a metal surface of a medical device.". Second, it is noted that the claims are examined *in light of* disclosure of specification and a specific embodiment disclosed in the specification is *not* to be incorporated into the claims that are currently under examination. In other words, the disclosure in the specification is not read into claims unless the claims recited the limitation. In this regard, it is noted that the limitations of newly added claim 39 and previously examined claim 3 are disclosed in paragraphs [0017] and [0021] of instant application (See US 2007/0092489, publication of instant patent application.). Third, the functional group of cross-linker SPDP disclosed in Figure 1B is *not* part of the modified CAR protein. Therefore, the

disclosure does not support Applicant's arguments that the modified protein is *directly* covalently bound to the metal surface because covalent bond is mediated through the disclosed cross linker SPDP.

In conclusion, the teachings by Kutryk et al. clearly anticipates claims 1, 8-10, 33, and 39 of instant application because Kutryk et al. teaches a composition comprising a medical device coated with one or more antibodies and one or more layers of a matrix, and the matrix may be covalently attached to the medical device, and antibodies may be covalently attached to the matrix using hetero- or homobifunctional cross-linking reagents (See abstract, lines 1-4, column 5, lines 15-55, column 12, and Figure 1, Kutryk et al.).

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 3, 33, and 34 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Kutryk et al.** (U.S. patent No. 7,037,332, issued May 2, 2006, filed on 03/15/2001) in view of **Xu et al.** (US patent 7,001,745, issued date 02/21/2006, filed on 09/30/1999). Applicant's arguments filed 03/09/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 12-13 of the office action mailed on 12/10/2008.

For clarity and completeness of this office action, the rejection for the reasons of record advanced on page 12-13 of the office action mailed on 12/10/2008, is revised below to address claim amendments filed on 03/09/2009.

Kutryk et al. teaches a composition comprising a metal medical device (for instance, a stent) coated with one or more antibodies and one or more layers of a matrix, and the matrix may be covalently attached to the medical device, and antibodies may be covalently attached to the matrix using hetero- or homobifunctional cross-linking reagents (See abstract, lines 1-4, column 5, lines 15-55, column 12, and Figure 1, Kutryk et al.).

Kutryk et al. does not teach the limitation "wherein the modified protein is covalently bound to the metal surface through thiol residue and a linker" recited in claim 3, and the limitation "wherein the fusion protein is generated through intein-mediated protein ligation" recited in claim 34, which depends from claim 33.

Xu et al. teaches intein mediated peptide ligation to generate a fusion protein of interest and a method for producing a semi-synthetic fusion protein *in vitro*, comprising the steps of producing a target protein fused to a protein splicing element (an intein) and selectively cleaving the fusion and ligating a synthetic protein or peptide at the C-terminal thioester of the target protein (See title and summary of invention, column 1, Xu et al.)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Kutryk et al. regarding a composition comprising a metal medical device coated with one or more antibodies and one or more layers of a matrix, and the matrix may be covalently attached to the medical device, and antibodies may be covalently attached to the matrix using hetero- or homobifunctional cross-linking reagents, with

the teaching of Xu et al. regarding generation of fusion protein of interest through intein-mediated protein ligation, to arrive at the claimed invention of claims 1, 3, 33, and 34.

One having ordinary skill in the art would have been motivated to combine the teachings of Kutryk et al. and Xu et al. because the intein-mediated protein ligation taught by Xu et al. provide a high-yield, semi-synthetic technique to allow in vitro fusion of a synthetic protein or peptide fragment to an expressed protein without limitation as to the size of the fused fragments.

There would have been a reasonable expectation of success given (i) successful demonstration of a metal medical device coated with one or more antibodies and one or more layers of a matrix, and the matrix being covalently attached to the medical device, and antibodies being covalently attached to the matrix using a cross-linking reagents by the teachings of Kutryk et al., and (ii) successful demonstration of direct ligation of a peptide to the thiester formed between VMA intein and maltose binding protein, by the teachings of Xu et al. (See Figure 3, lines 48-50, column 2, Xu et al.)

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments

Applicant argues that, as discussed above, Kutryk does not disclose a composition comprising a metal surface and a modified protein, wherein the modified protein is covalently bound to the metal surface. Applicant argues that Xu discloses intein-mediated peptide ligation to generate a fusion protein; however, Xu does not disclose a composition comprising a metal surface and a modified protein, wherein the modified protein is covalently bound to the metal surface. Applicant argues that, because Xu cannot compensate for the elements missing in

Kutryk, neither Xu nor Kutryk, alone or in combination, renders claims 1, 3, 33 or 34 unpatentable (See bridging paragraph, pages 10-11 of Applicant's remarks filed on 03/09/2009).

Response to Applicant's arguments

The reasons why Kutryk et al. teaches the limitation "wherein the modified protein is covalently bound to the metal surface" have been documented in the maintained rejection of claims 1, 8-10, and 33 and rejection of newly added claim 39 under 35 U.S.C. 102(e) as being anticipated by Kutryk et al. Xu et al. is relied on for disclosure of the limitation "wherein the modified protein is covalently bound to the metal surface through thiol residue and a linker" recited in claim 3, and the limitation "wherein the fusion protein is generated through intein-mediated protein ligation" recited in claim 34, which depends from claim 33.

8. Claims 1, 33, and 35-37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Kutryk et al.** (U.S. patent No. 7,037,332, issued May 2, 2006, filed on 03/15/2001) in view of **Li et al.** (US patent 6,524,572, issued date 02/25/2003, filed on 09/26/2000). Applicant's arguments filed 03/09/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 14-15 of the office action mailed on 12/10/2008.

For clarity and completeness of this office action, the rejection for the reasons of record advanced on page 14-15 of the office action mailed on 12/10/2008, is revised below to address claim amendments filed on 03/09/2009.

Kutryk et al. teaches a composition comprising a metal medical device (for instance, a stent) coated with one or more antibodies and one or more layers of a matrix, and the matrix may be covalently attached to the medical device, and antibodies may be covalently attached to the matrix using hetero- or homobifunctional cross-linking reagents (See abstract, lines 1-4, column 5, lines 15-55, column 12, and Figure 1, Kutryk et al.).

Kutryk et al. does not teach "wherein the fusion protein comprises at least a fragment of a CAR protein and a receptor targeting ligand" recited in claim 35, the fragment of the CAR protein recited in claim 36, and the receptor targeting ligand recited in claim 37.

Li teaches the fusion protein comprises extracellular domain of CAR/Hinge/protein A ligand, and Li develops a strategy using adenovirus as an example to demonstrate the strategy of using the fusion protein to re-direct viral tropism (See abstract and Figure 1, Li). Li teaches that any extracellular domain of a viral receptor that is a membrane protein or membrane peptide can be used to replace extracellular domain of CAR and can be inserted as a part of the fusion protein ligand for targeting (See lines 20-24, column 8, Li). Li teaches that Arg-Gly-Asp (RGD) motif of viral pentose protein binds to integrins of cell membrane and this binding activates virus internalization via receptor-mediated endocytosis (lines 53-58, column 1, Li)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Kutryk et al. regarding a composition comprising a metal medical device coated with one or more antibodies and one or more layers of a matrix, and the matrix may be covalently attached to the medical device, and antibodies may be covalently attached to the matrix using hetero- or homobifunctional cross-linking reagents, with

the teaching of Li et al. regarding fusion protein comprises extracellular domain of CAR/receptor targeting ligand, to arrive at the claimed invention of claims 1, 33, and 35-37.

One having ordinary skill in the art would have been motivated to combine the teachings of Kutryk et al. and Li et al. because the fusion protein taught by Li can target specifically the receptor of interest present on cell membrane in the context of using viral vector to deliver therapeutic agent via the metal surface of a medical device, for instance, a stent taught by Kutryk et al.

There would have been a reasonable expectation of success given (i) successful demonstration of a metal medical device coated with one or more antibodies and one or more layers of a matrix, and the matrix being covalently attached to the medical device, and antibodies being covalently attached to the matrix using a cross-linking reagents by the teachings of Kutryk et al., and (ii) successful construction of the fusion protein comprises extracellular domain of CAR/receptor targeting ligand, by the teachings of Li.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments

Applicant argues that, as discussed above, Kutryk does not disclose a composition comprising a metal surface and a modified protein, wherein the modified protein is covalently bound to the metal surface. Applicant argues that, Li does not disclose a composition comprising a metal surface and a modified protein, wherein the modified protein is covalently bound to the metal surface. Applicant argues that because Li cannot compensate for the elements

missing in Kutryk, Li and Kutryk, alone or in combination, do not render claims 1, 33, and 35-37 obvious.

Response to Applicant's arguments

The reasons why Kutryk et al. teaches the limitation "wherein the modified protein is covalently bound to the metal surface" have been documented in the maintained rejection of claims 1, 8-10, and 33 and rejection of newly added claim 39 under 35 U.S.C. 102(e) as being anticipated by Kutryk et al. Li et al. is relied on for disclosure of "wherein the fusion protein comprises at least a fragment of a CAR protein and a receptor targeting ligand" recited in claim 35, the fragment of the CAR protein recited in claim 36, and the receptor targeting ligand recited in claim 37.

Conclusion

9. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent

examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

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